(FILE 'HOME' ENTERED AT 07:12:31 ON 05 MAR 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 07:12:52 ON 05 MAR 2004

		E	HUANG H/AU
L1	438	S	E22-24
		E	NAGANE MOTOO/AU
L2	50	S	E3
		E	CAVENEE WEBSTER/AU
L3	279	S	E2-5
L4	629	S	L1 OR L2 OR L3
L5	369	DUP	REM L4 (260 DUPLICATES REMOVED)
L6	223162	S	EPIDERMAL
L7	41	S	L5 AND L6
L8	327047	S	APOPTOSIS
L9	17866	S	EGFR
L10	409788	S	TYROSINE
L11	5710	S	TYRPHOSTIN
L12	29	S	L7 AND (L8 OR L9 OR L10 OR L11)

L12 ANSWER 1 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003248431 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12734385
TITLE: **Epidermal** growth factor receptor signaling intensity determines intracellular protein interactions, ubiquitination, and internalization.
AUTHOR: Schmidt Mirko H H; Furnari Frank B; **Cavenee Webster K**; Bogler Oliver
CORPORATE SOURCE: William and Karen Davidson Laboratory of Brain Tumor Biology, Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA.
CONTRACT NUMBER: CA-R01-84109 (NCI)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 May 27) 100 (11) 6505-10. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030529
Last Updated on STN: 20030717
Entered Medline: 20030716

AB Ligand activation of the **epidermal** growth factor receptor (**EGFR**) causes the binding of Cbls, which leads to **EGFR** polyubiquitination and internalization through endophilin complexes that contain the adaptor protein SH3-domain encoding, expressed in tumorigenic astrocytes/Cbl-interacting protein of 85 kDa/regulator of ubiquitous kinase (SETA/CIN85/Ruk). In cells grown at high density, high levels of SETA interfered in the recruitment of Casitas B-lineage (Cbl) proteins to the **EGFR** and reduced its polyubiquitination, suggesting that SETA has a regulatory function in the formation of the **EGFR** -Cbl-endophilin complex and in **EGFR** down-regulation. In a situation where there is **EGFR** signaling but no internalization or down-regulation, as is the case with the **EGFR** with exons 2-7 deleted (DeltaEGFR) oncogene, these proteins were absent altogether. By using mAb 806, which recognizes an **EGFR**-activation state and preferentially immunoprecipitates DeltaEGFR, we show that DeltaEGFR did not interact with Cbls, SETA, or endophilin A1, providing a mechanistic explanation for its lack of internalization. As would be expected by the absence of Cbl proteins in the DeltaEGFR complex, the mutant receptor was also not polyubiquitinated. The intracellular C terminus and **tyrosine** autophosphorylation pattern of DeltaEGFR are similar to wild-type **EGFR**, but it signals at a lower intensity as determined by levels of **EGFR** phosphotyrosine. To test the implication that the lack of interaction with the Cbl-SETA-endophilin complex is because of differences in signal intensity, **EGFR** -expressing cells were treated with **tyrphostin** AG1478 **EGFR** inhibitor. Attenuation of wild-type **EGFR** signal to levels similar to that found in DeltaEGFR resulted in the dissociation of SETA and Cbl proteins and a concomitant attenuation of receptor internalization.

L12 ANSWER 2 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003051710 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12515857
TITLE: A monoclonal antibody recognizing human cancers with amplification/overexpression of the human **epidermal** growth factor receptor.
COMMENT: Erratum in: Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):2163. Cavanee Webster K [corrected to Cavenee Webster K]
AUTHOR: Jungbluth Achim A; Stockert Elisabeth; **Huang H J Su** ; Collins Vincent P; Coplan Keren; Iversen Kristin; Kolb Denise; Johns Terrance J; Scott Andrew M; Gullick William J; Ritter Gerd; Cohen Leonard; Scanlan Matthew J; **Cavenee Webster K**; Old Lloyd J
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.. jungblua@mskcc.org
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 Jan 21) 100 (2) 639-44. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030204
Last Updated on STN: 20030402
Entered Medline: 20030224

AB **Epidermal** growth factor receptor (**EGFR**) has attracted considerable attention as a target for cancer therapy. Wild-type (wt) **EGFR** is amplified/overexpressed in a number of tumor types, and several mutant forms of the coding gene have been found, with DeltaEGFR, a deletion mutation lacking exons 2-7 of the external domain, being the most common and particularly associated with glioblastoma. We generated monoclonal antibodies (mAbs) against NR6(DeltaEGFR) (mouse fibroblast line NR6 transfected with DeltaEGFR). mAb 806 with selective reactivity for NR6(DeltaEGFR) in mixed hemadsorption assays, fluorescence-activated cell sorting, Western blot, and immunohistochemistry was analyzed in detail and compared with mAbs 528 (anti-wtEGFR) and DH8.3 (anti-DeltaEGFR). In xenograft tumors and molecularly pretyped glioblastomas, the reactivity pattern was as follows: 528 reactive with amplified and nonamplified wtEGFR; DH8.3 reactive with DeltaEGFR; and 806 reactive with amplified/overexpressed wtEGFR (with or without DeltaEGFR). In normal tissues, 528 but not DH8.3 or 806 was widely reactive with many organs, e.g., liver expressing high **EGFR** levels. In glioblastoma and non-CNS tumor panels, 806 was reactive with a high proportion of glioblastomas and a substantial number of epithelial cancers of lung and of head and neck. DH8.3 reactivity was restricted to DeltaEGFR-positive glioblastoma. Thus, 806 represents a category of mAbs that recognizes tumors with **EGFR** amplification/overexpression but not normal tissues or tumors with normal **EGFR** levels. Our study also indicates that DeltaEGFR is restricted to glioblastoma, in contrast to other reports that this mutation is found in tumors outside the brain.

L12 ANSWER 3 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002677807 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12438278
TITLE: Mutant **epidermal** growth factor receptor signaling down-regulates p27 through activation of the phosphatidylinositol 3-kinase/Akt pathway in glioblastomas.
AUTHOR: Narita Yoshitaka; **Nagane Motoo**; Mishima Kazuhiko; **Huang H-J Su**; Furnari Frank B; **Cavenee Webster K**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, San Diego Branch, University of California at San Diego, La Jolla, California 92093-0660, USA.
SOURCE: Cancer research, (2002 Nov 15) 62 (22) 6764-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021120
Last Updated on STN: 20021218
Entered Medline: 20021217

AB Alterations of the **epidermal** growth factor receptor (**EGFR**) gene are common in some forms of cancer and the most frequent is a deletion of exons 2-7. We have previously shown that this mutant receptor, called DeltaEGFR, confers enhanced tumorigenicity to glioblastoma cells through elevated proliferation and reduced apoptotic rates of the tumor cells in vivo. To understand the molecular mechanisms that underlie DeltaEGFR-enhanced proliferation, we examined the gene products that control cell cycle progression. We found that levels of the cyclin-dependent kinase (CDK) inhibitor, p27, were lower in U87MG.DeltaEGFR tumors than in parental U87MG or control U87MG.DK tumors. Consequently, CDK2-cyclin A activity was also elevated, concomitant with the RB protein hyperphosphorylation. In addition, activated phosphatidylinositol 3-kinase (PI3-K) and phosphorylated Akt levels were also elevated in the U87MG.DeltaEGFR tumors. U87MG.DeltaEGFR cells failed to arrest in G(1) in response to serum starvation in vitro and while maintaining high levels of PI3-K activity and hyperphosphorylated RB. Treatment of U87MG.DeltaEGFR cells with LY294002, a PI3-K inhibitor, caused reduced levels of phosphorylated Akt and concomitantly up-regulated levels of p27. Expression of a kinase dead dominant-negative Akt mutant in the U87MG.DeltaEGFR cells similarly resulted in up-regulation of p27 and down-regulation of tumorigenicity in vivo. These results suggest that

the constitutively active DeltaEGFR can enhance cell proliferation in part by down-regulation of p27 through activation of the PI3-K/Akt pathway. This pathway may represent another therapeutic target for treatment of those aggressive glioblastomas expressing DeltaEGFR.

L12 ANSWER 4 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002185139 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11920591
TITLE: Novel monoclonal antibody specific for the de2-7 **epidermal** growth factor receptor (**EGFR**) that also recognizes the **EGFR** expressed in cells containing amplification of the **EGFR** gene.
AUTHOR: Johns Terrance G; Stockert Elisabeth; Ritter Gerd; Jungbluth Achim A; **Huang H-J Su**; **Cavenee Webster K**; Smyth Fiona E; Hall Cathrine M; Watson Nadine; Nice Edouard C; Gullick William J; Old Lloyd J; Burgess Antony W; Scott Andrew M
CORPORATE SOURCE: Tumour Targeting Program, Ludwig Institute for Cancer Research, Melbourne, Australia.. Terry.Johns@ludwig.edu.au
SOURCE: International journal of cancer. Journal international du cancer, (2002 Mar 20) 98 (3) 398-408. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020417
Entered Medline: 20020416

AB In some respects, the **EGFR** appears to be an attractive target for tumor-targeted antibody therapy: it is overexpressed in many types of epithelial tumor and inhibition of signaling often induces an anti-tumor effect. The use of **EGFR** specific antibodies, however, may be limited by uptake in organs that have high endogenous levels of the wild type **EGFR** such as the liver. The de2-7 **EGFR** (or EGFRvIII) is a naturally occurring extracellular truncation of the **EGFR** found in a number of tumor types including glioma, breast, lung and prostate. Antibodies directed to this tumor specific variant of the **EGFR** provide an alternative targeting strategy, although the lower proportion of tumors that express the de2-7 **EGFR** restricts this approach. We describe a novel monoclonal antibody (MAb 806) that potentially overcomes the difficulties associated with targeting the **EGFR** expressed on the surface of tumor cells. MAb 806 bound to de2-7 **EGFR** transfected U87MG glioma cells (U87MG.Delta 2-7) with high affinity (approximately 1 x 10(9) M(-1)), but did not bind parental cells that express the wild type **EGFR**. Consistent with this observation, MAb 806 was unable to bind a soluble version of the wild type **EGFR** containing the extracellular domain. In contrast, immobilization of this extracellular domain to ELISA plates induced saturating and dose response binding of MAb 806, suggesting that MAb 806 can bind the wild type **EGFR** under certain conditions. MAb 806 also bound to the surface of A431 cells, which due to an amplification of the **EGFR** gene express large amounts of the **EGFR**. Interestingly, MAb 806 only recognized 10% of the total **EGFR** molecules expressed by A431 cells and the binding affinity was lower than that determined for the de2-7 **EGFR**. MAb 806 specifically targeted U87MG.Delta 2-7 and A431 xenografts grown in nude mice with peak levels in U87MG.Delta 2-7 xenografts detected 8 h after injection. No specific targeting of parental U87MG xenografts was observed. Following binding to U87MG.Delta 2-7 cells, MAb 806 was rapidly internalized by macropinocytosis and subsequently transported to lysosomes, a process that probably contributes to the early targeting peak observed in the xenografts. Thus, MAb 806 can be used to target tumor cells containing amplification of the **EGFR** gene or de2-7 **EGFR** but does not bind to the wild type **EGFR** when expressed on the cell surface.

L12 ANSWER 5 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2002044084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11770895
TITLE: CD95-mediated **apoptosis** of human glioma cells: modulation by **epidermal** growth factor receptor activity.
AUTHOR: Steinbach Joachim P; Supra Petra; **Huang H-J Su**;

Cavenee Webster K; Weller Michael
CORPORATE SOURCE: Department of Neurology, University of Tubingen, School of Medicine, Germany.. joachim.steinbach@uni-tuebingen.de
SOURCE: Brain pathology (Zurich, Switzerland), (2002 Jan) 12 (1) 12-20.
Journal code: 9216781. ISSN: 1015-6305.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020531
Entered Medline: 20020530

AB The death ligands CD95L and Apo2L/TRAIL are promising investigational agents for the treatment of malignant glioma. **EGFR** is overexpressed in a significant proportion of malignant gliomas in vivo. Here, we report that CD95L-induced cell death is enhanced by **EGFR** inhibition using tyrphostine AG1478 in 7 of 12 human malignant glioma cell lines. Conversely, CD95-mediated and Apo2L-induced cell death are both inhibited by overexpression of **EGFR** in LN-229 cells. CD95L-induced cell death augmented by AG1478 is accompanied by enhanced processing of caspase 8. LN-229 cells overexpressing the viral caspase inhibitor, crm-A, are not sensitized to CD95L-induced cell death by AG1478, indicating that **EGFR** exerts its antiapoptotic properties through a caspase 8-dependent pathway. These data define a modulatory effect of **EGFR**-activity on death ligand-induced **apoptosis** and indicate that **EGFR** inhibition is likely to improve the efficacy of death ligand-based cancer therapies. Furthermore, it is tempting to speculate that **EGFR** amplification protects tumor cells from death ligand-mediated host immune responses in vivo and that **EGFR**'s effects on death receptor-mediated **apoptosis** may explain the anti-tumor effects of non-cytotoxic, unarmed anti-**EGFR** family antibodies.

L12 ANSWER 6 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2001685099 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11514572
TITLE: The protein **tyrosine** phosphatase TCPTP suppresses the tumorigenicity of glioblastoma cells expressing a mutant **epidermal** growth factor receptor.
AUTHOR: Klingler-Hoffmann M; Fodero-Tavoletti M T; Mishima K; Narita Y; Cavenee W K; Furnari F B; **Huang H J**; Tiganis T
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Monash University, Victoria 3800, Australia.
SOURCE: Journal of biological chemistry, (2001 Dec 7) 276 (49) 46313-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011204
Last Updated on STN: 20020125
Entered Medline: 20020110

AB Glioblastoma multiforme (GBM) is the most aggressive type of glioma and GBMs frequently contain amplifications or mutations of the **EGFR** gene. The most common mutation results in a truncated receptor **tyrosine** kinase known as Delta **EGFR** that signals constitutively and promotes GBM growth. Here, we report that the 45-kDa variant of the protein **tyrosine** phosphatase TCPTP (TC45) can recognize Delta **EGFR** as a cellular substrate. TC45 dephosphorylated Delta **EGFR** in U87MG glioblastoma cells and inhibited mitogen-activated protein kinase ERK2 and phosphatidylinositol 3-kinase signaling. In contrast, the substrate-trapping TC45-D182A mutant, which is capable of forming stable complexes with TC45 substrates, suppressed the activation of ERK2 but not phosphatidylinositol 3-kinase. TC45 inhibited the proliferation and anchorage-independent growth of Delta **EGFR** cells but TC45-D182A only inhibited cellular proliferation. Notably, neither TC45 nor TC45-D182A inhibited the proliferation of U87MG cells that did not express Delta **EGFR**. Delta **EGFR** activity was necessary for the activation of ERK2, and pharmacological inhibition of ERK2 inhibited the proliferation of Delta **EGFR** -expressing U87MG cells. Expression of either TC45 or TC45-D182A also

suppressed the growth of Delta **EGFR**-expressing U87MG cells in vivo and prolonged the survival of mice implanted intracerebrally with these tumor cells. These results indicate that TC45 can inhibit the Delta **EGFR**-mediated activation of ERK2 and suppress the tumorigenicity of Delta **EGFR**-expressing glioblastoma cells in vivo.

L12 ANSWER 7 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2001518905 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11565870
TITLE: Human glioblastoma xenografts overexpressing a tumor-specific mutant **epidermal** growth factor receptor sensitized to cisplatin by the AG1478 **tyrosine** kinase inhibitor.
AUTHOR: Nagane M; Narita Y; Mishima K; Levitzki A; Burgess A W; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Ludwig Institute for Cancer Research--San Diego, Department of Medicine, Center for Molecular Genetics, and Cancer Center, University of California at San Diego, La Jolla 92093-0660, USA.
SOURCE: Journal of neurosurgery, (2001 Sep) 95 (3) 472-9. Journal code: 0253357. ISSN: 0022-3085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20011008
Entered Medline: 20011004

AB OBJECT: Activation of signaling by the **epidermal** growth factor receptor (**EGFR**) through gene amplification or rearrangement is common in human malignancy, especially in a large fraction of de novo glioblastomas multiforme (GBMs). The most common mutant **EGFR**, (AEGFR, also known as de2-7 **EGFR** and EGFRvIII) lacks a portion of the extracellular domain, enhances tumorigenicity in vivo, and causes resistance to the chemotherapeutic drug cisplatin (CDDP). This resistance is due to the suppression of CDDP-induced **apoptosis** by the constitutively active **tyrosine** kinase activity of the receptor. The authors have investigated whether inhibition of AEGFR signaling by the **tyrosine** kinase inhibitor, **tyrphostin** AG1478, could sensitize tumor xenografts to CDDP and, thereby, enhance its therapeutic efficacy in animals. METHODS: Nude mice were inoculated either subcutaneously or intracerebrally with human GBM cells expressing AEGFR and were then systemically treated with CDDP and/or AG1478. Tumor volumes were monitored and tumor sections were analyzed by using terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assays or MIB-1 staining. Expression of AEGFR, but not wild-type **EGFR**, conferred CDDP resistance to the cells in vivo. Inhibition of receptor signaling by the **EGFR**-specific **tyrosine** kinase inhibitor, AG1478. sensitized the xenografts to the cytotoxic effects of CDDP. This combined CDDP/AG1478 treatment significantly suppressed growth of subcutaneous xenografts in nude mice in a synergistic manner ($p < 0.01$ compared with vehicle control) without causing generalized toxicity, whereas treatments with CDDP or AG1478 alone were ineffective. The synergistic growth suppression by the CDDP/AG1478 combination was not observed in xenografts overexpressing wild-type **EGFR** or kinase-deficient AEGFR. The combined CDDP/ AG1478 treatment induced tumor growth suppression, which correlated with increased **apoptosis** and reduced proliferation. This treatment also extended the life span of mice bearing intracerebral xenografts ($p < 0.01$ compared with controls). CONCLUSIONS: The results of this study may provide the basis for the development of a novel and safe therapeutic strategy for the very aggressive AEGFR-expressing GBM.

L12 ANSWER 8 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2001407885 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11454673
TITLE: Growth suppression of intracranial xenografted glioblastomas overexpressing mutant **epidermal** growth factor receptors by systemic administration of monoclonal antibody (mAb) 806, a novel monoclonal antibody directed to the receptor.
COMMENT: Erratum in: Cancer Res 2001 Oct 15;61(20):7703-5
AUTHOR: Mishima K; Johns T G; Luwor R B; Scott A M; Stockert E; Jungbluth A A; Ji X D; Suvarna P; Voland J R; Old L J; **Huang H J**; Cavenee W K

CORPORATE SOURCE: Ludwig Institute for Cancer Research, San Diego Branch, University of California at San Diego, La Jolla, California 92093-0660, USA.
SOURCE: Cancer research, (2001 Jul 15) 61 (14) 5349-54. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20020313
Entered Medline: 20010802

AB A mutant **epidermal** growth factor receptor (variously called DeltaEGFR, de2-7 **EGFR**, or EGFRvIII) containing a deletion of 267 amino acids of the extracellular domain is frequently highly expressed in human malignant gliomas and has been reported for cancers of the lung, breast, and prostate. We tested the efficacy of a novel monoclonal anti-DeltaEGFR antibody, mAb 806, on the growth of intracranial xenografted gliomas in nude mice. Systemic treatment with mAb 806 significantly reduced the volume of tumors and increased the survival of mice bearing xenografts of U87 MG.DeltaEGFR, LN-Z308.DeltaEGFR, or A1207.DeltaEGFR gliomas, each of which expresses high levels of DeltaEGFR. In contrast, mAb 806 treatment was ineffective with mice bearing the parental U87 MG tumors, which expressed low levels of endogenous wild-type **EGFR**, or U87 MG.DK tumors, which expressed high levels of kinase-deficient DeltaEGFR. A slight increase of survival of mice xenografted with a wild-type **EGFR**-overexpressing U87 MG glioma (U87 MG.wtEGFR) was effected by mAb 806 concordant with its weak cross-reactivity with such cells. Treatment of U87 MG.DeltaEGFR tumors in mice with mAb 806 caused decreases in both tumor growth and angiogenesis, as well as increased **apoptosis**. Mechanistically, in vivo mAb 806 treatment resulted in reduced phosphorylation of the constitutively active DeltaEGFR and caused down-regulated expression of the apoptotic protector, Bcl-XL. These data provide preclinical evidence that mAb 806 treatment may be a useful biotherapeutic agent for those aggressive gliomas that express DeltaEGFR.

L12 ANSWER 9 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2001403001 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11454674
TITLE: Monoclonal antibody 806 inhibits the growth of tumor xenografts expressing either the de2-7 or amplified **epidermal** growth factor receptor (**EGFR**) but not wild-type **EGFR**.
AUTHOR: Luwor R B; Johns T G; Murone C; **Huang H J**; Cavenee W K; Ritter G; Old L J; Burgess A W; Scott A M
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Melbourne Branch, Tumour Targeting Program, Austin and Repatriation Medical Centre, Heidelberg 3084, Victoria, Australia.
SOURCE: Cancer research, (2001 Jul 15) 61 (14) 5355-61. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB The monoclonal antibody (mAb) 806 was raised against the delta2-7 **epidermal** growth factor receptor (de2-7 **EGFR** or EGFRvIII), a truncated version of the **EGFR** commonly expressed in glioma. Unexpectedly, mAb 806 also bound the **EGFR** expressed by cells exhibiting amplification of the **EGFR** gene but not to cells or normal tissue expressing the wild-type receptor in the absence of gene amplification. The unique specificity of mAb 806 offers an advantage over current **EGFR** antibodies, which all display significant binding to the liver and skin in humans. Therefore, we examined the antitumor activity of mAb 806 against human tumor xenografts grown in nude mice. The growth of U87 MG xenografts, a glioma cell line that endogenously expresses approximately 10(5) **EGFRs** in the absence of gene amplification, was not inhibited by mAb 806. In contrast, mAb 806 significantly inhibited the growth of U87 MG xenografts transfected with the de2-7 **EGFR** in a dose-dependent manner using both preventative and established tumor models. Significantly, U87 MG cells

transfected with the wild-type **EGFR**, which increased expression to approximately 10(6) **EGFRs**/cell and mimics the situation of gene amplification, were also inhibited by mAb 806 when grown as xenografts in nude mice. Xenografts treated with mAb 806 all displayed large areas of necrosis that were absent in control tumors. This reduced xenograft viability was not mediated by receptor down-regulation or clonal selection because levels of antigen expression were similar in control and treated groups. The antitumor effect of mAb 806 was not restricted to U87 MG cells because the antibody inhibited the growth of new and established A431 xenografts, a cell line expressing >10(6) **EGFRs**/cell. This study demonstrates that mAb 806 possesses significant antitumor activity.

L12 ANSWER 10 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2001142891 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11164186
TITLE: Aberrant receptor signaling in human malignant gliomas: mechanisms and therapeutic implications.
AUTHOR: Nagane M; Lin H; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, San Diego Branch, 3080 CMM-East, 9500 Gilman Drive, La Jolla, CA 92093-0660, USA.
SOURCE: Cancer letters, (2001 Jan) 162 Suppl S17-S21. Ref: 32 Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404 Last Updated on STN: 20010404 Entered Medline: 20010308
AB Alterations of the **epidermal** growth factor receptor (**EGFR**) occur frequently in malignant gliomas through gene amplification or rearrangement, especially in a large fraction of de novo type glioblastomas. The most common of these mutant **EGFRs** (variously named de2-7 **EGFR**, deltaEGFR or EGFRvIII) lacks a portion of the extracellular ligand-binding domain. Here, we review the evidence that shows that expression of deltaEGFR bestows in vivo growth advantages to human glioma cells through its constitutively active **tyrosine** kinase activity. Thus, deltaEGFR may provide a novel therapeutic target for the most aggressive type of glioblastoma.

L12 ANSWER 11 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1998245148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9576951
TITLE: Drug resistance of human glioblastoma cells conferred by a tumor-specific mutant **epidermal** growth factor receptor through modulation of Bcl-XL and caspase-3-like proteases.
AUTHOR: Nagane M; Levitzki A; Gazit A; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla, CA 92093-0660, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1998 May 12) 95 (10) 5724-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708 Last Updated on STN: 20000303 Entered Medline: 19980619
AB Alterations of the **epidermal** growth factor receptor (**EGFR**) gene occur frequently in human malignant gliomas. The most common of these is deletion of exons 2-7, resulting in truncation of the extracellular domain (DeltaEGFR or EGFRvIII), which occurs in a large fraction of de novo malignant gliomas (but not in progressive tumors or those lacking p53 function) and enhances tumorigenicity, in part by decreasing **apoptosis** through up-regulation of Bcl-XL. Here, we demonstrate that the DeltaEGFR concomitantly confers resistance to the chemotherapeutic drug cisplatin (CDDP) by suppression of CDDP-induced **apoptosis**. Expression of Bcl-XL was elevated in U87MG.DeltaEGFR

cells prior to and during CDDP treatment, whereas it decreased considerably in CDDP-treated parental cells. CDDP-induced activation of caspase-3-like proteases was suppressed significantly in U87MG.DeltaEGFR cells. These responses were highly specific to constitutively kinase-active DeltaEGFR, because overexpression of kinase-deficient DeltaEGFR (DK) or wild-type **EGFR** had no such effects. Correspondingly, DeltaEGFR specific **tyrosine** kinase inhibitors reduced Bcl-XL expression and potentiated CDDP-induced **apoptosis** in U87MG.DeltaEGFR cells. Ectopic overexpression of Bcl-XL in parental U87MG cells also resulted in suppression of both caspase activation and **apoptosis** induced by CDDP. These results may have important clinical implications for the use of CDDP in the treatment of those malignant gliomas expressing DeltaEGFR.

L12 ANSWER 12 OF 29 MEDLINE on STN
ACCESSION NUMBER: 97051028 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8895767
TITLE: A common mutant **epidermal** growth factor receptor confers enhanced tumorigenicity on human glioblastoma cells by increasing proliferation and reducing **apoptosis** .
AUTHOR: Nagane M; Coufal F; Lin H; Bogler O; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla 92093-0660, USA.
CONTRACT NUMBER: 5-T32-NS 07342 (NINDS)
SOURCE: Cancer research, (1996 Nov 1) 56 (21) 5079-86. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970106

AB Alterations of the **EGFR** gene occur frequently in human gliomas where the most common is an in-frame deletion of exons 2-7 from the extracellular domain, resulting in a truncated mutant receptor (deltaEGFR or de 2-7 **EGFR**). We previously demonstrated that introduction of deltaEGFR into human U87MG glioblastoma cells (U87MG.deltaEGFR) conferred remarkably enhanced tumorigenicity in vivo. Here, we show by cell-mixing experiments that the enhanced tumorigenicity conferred by deltaEGFR is attributable to a growth advantage intrinsic to cells expressing the mutant receptor. We analyzed the labeling index of the proliferation markers Ki-67 and bromodeoxyuridine and found that tumors derived from U87MG.deltaEGFR cells had significantly higher labeling indexes than those of tumors derived from U87MG cells that were either naive, expressed kinase-deficient mutants of deltaEGFR, or overexpressed exogenous wild-type **EGFR**. We also utilized terminal deoxynucleotidyl transferase-mediated nick end-labeling assays and showed that the apoptotic index of U87MG.deltaEGFR tumors was more than 4-fold lower than that of parental U87MG tumors. This decrease in cell death was inversely correlated with the expression level of Bcl-X(L), a negative regulator of **apoptosis**, which was more than 3-fold higher in U87MG.deltaEGFR-derived tumors than in those derived from parental cells. Similar observations were obtained in vitro in serum-free conditions. These results suggest that deltaEGFR exerts its pronounced enhancement of glioblastoma tumorigenicity by stimulating proliferation and inhibiting **apoptosis** and that the effects are directly attributable to its constitutively active signal.

L12 ANSWER 13 OF 29 MEDLINE on STN
ACCESSION NUMBER: 96354597 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8752145
TITLE: **Tyrphostin** AG 1478 preferentially inhibits human glioma cells expressing truncated rather than wild-type **epidermal** growth factor receptors.
AUTHOR: Han Y; Caday C G; Nanda A; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Department of Neurosurgery, Louisiana State University Medical Center, Shreveport 71130, USA.
SOURCE: Cancer research, (1996 Sep 1) 56 (17) 3859-61. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961015
Last Updated on STN: 20000303
Entered Medline: 19960930

AB The effects of a new **epidermal** growth factor receptor (**EGFR**) **tyrosine** kinase inhibitor, **tyrphostin** AG 1478, were tested on three related human glioma cell lines: U87MG, which expressed endogenous wild-type (wt) **EGFR**, and two retrovirally infected U87MG cell populations which over-expressed either wt (U87MG.wtEGFR) or truncated **EGFR** (U87MG. delta **EGFR**). Although AG 1478 inhibited cell growth, DNA synthesis, **EGFR** **tyrosine** kinase activity, and receptor autophosphorylation of each cell line in a dose-dependent manner, it was significantly more potent in U87MG. delta **EGFR** cells than in the other two cell lines. The increased inhibitory response of U87MG. delta **EGFR** cells was due to a greater sensitivity of the constitutively autophosphorylated Mr 140,000 and 155,000 delta **EGFR** species to AG 1478. These results suggest that AG 1478 is a relatively specific inhibitor of the delta **EGFR**, and this finding may have important therapeutic implications since the delta **EGFR** occurs frequently in glioblastomas and in breast, lung, and ovarian cancers.

L12 ANSWER 14 OF 29 MEDLINE on STN
ACCESSION NUMBER: 94329589 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8052651
TITLE: A mutant **epidermal** growth factor receptor common in human glioma confers enhanced tumorigenicity.
AUTHOR: Nishikawa R; Ji X D; Harmon R C; Lazar C S; Gill G N; Cavenee W K; **Huang H J**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, La Jolla, CA 92093-0660.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994 Aug 2) 91 (16) 7727-31. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940914
Last Updated on STN: 20000303
Entered Medline: 19940902

AB The development and neoplastic progression of human astrocytic tumors appears to result through an accumulation of genetic alterations occurring in a relatively defined order. One such alteration is amplification of the **epidermal** growth factor receptor (**EGFR**) gene. This episomal amplification occurs in 40-50% of glioblastomas, which also normally express endogenous receptors. Moreover, a significant fraction of amplified genes are rearranged to specifically eliminate a DNA fragment containing exons 2-7 of the gene, resulting in an in-frame deletion of 801 bp of the coding sequence of the extracellular domain. Here we used retroviral transfer of such a mutant receptor (de 2-7 **EGFR**) into glioblastoma cells expressing normal endogenous receptors to test whether the mutant receptor was able to augment their growth and malignancy. Western blotting analysis showed that these cells expressed endogenous **EGFR** of 170 kDa as well as the exogenous de 2-7 **EGFR** of 140-155 kDa. Although holo-**EGFRs** were phosphorylated on **tyrosine** residues only after exposure of the cells to ligand, de 2-7 **EGFRs** were constitutively phosphorylated. In tissue culture neither addition of EGF nor expression of the mutant **EGFR** affected the rate of cell growth. However, when cells expressing mutant **EGFR** were implanted into nude mice subcutaneously or intracerebrally, tumorigenic capacity was greatly enhanced. These results suggest that a tumor-specific alteration of the **EGFR** plays a significant role in tumor progression perhaps by influencing interactions of tumor cells with their microenvironment in ways not easily assayed in vitro.

L12 ANSWER 15 OF 29 EMBASE on STN
ACCESSION NUMBER: 97036644 EMBASE
DOCUMENT NUMBER: 1997036644
TITLE: The enhanced tumorigenic activity of a mutant **epidermal** growth factor receptor common in human cancers is mediated by threshold levels of constitutive

tyrosine phosphorylation and unattenuated signaling.

AUTHOR: **Huang H.-J.S.**; Nagane M.; Klingbeil C.K.; Hong Lin; Nishikawa R.; Ji X.- D.; Huang C.-M.; Gill G.N.; Wiley H.S.; Cavenee W.K.

CORPORATE SOURCE: H.-J.S. Huang, Ludwig Institute for Cancer Research, 9500 Gilman Dr, San Diego, CA 92093-0660, United States. hhuang@ucsd.edu

SOURCE: Journal of Biological Chemistry, (1997) 272/5 (2927-2935). Refs: 72
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Deregulation of signaling by the **epidermal** growth factor receptor (**EGFR**) is common in human malignancy progression. One mutant **EGFR** (variously named Δ **EGFR**, de2-7 **EGFR**, or EGFRvIII), which occurs frequently in human cancers, lacks a portion of the extracellular ligand-binding domain due to genomic deletions that eliminate exons 2 to 7 and confers a dramatic enhancement of brain tumor cell tumorigenicity in vivo. In order to dissect the molecular mechanisms of this activity, we analyzed location, autophosphorylation, and attenuation of the mutant receptors. The mutant receptors were expressed on the cell surface and constitutively autophosphorylated at a significantly decreased level compared with wild-type **EGFR** activated by ligand treatment. Unlike wild-type **EGFR**, the constitutively active Δ **EGFR** were not down- regulated, suggesting that the altered conformation of the mutant did not result in exposure of receptor sequence motifs required for endocytosis and lysosomal sorting. Mutational analysis showed that the enhanced tumorigenicity was dependent on intrinsic **tyrosine** kinase activity and was mediated through the carboxyl terminus. In contrast with wild-type receptor, mutation of any major **tyrosine** autophosphorylation site abolished these activities suggesting that the biological functions of Δ **EGFR** are due to low constitutive activation with mitogenic effects amplified by failure to attenuate signaling by receptor down-regulation.

L12 ANSWER 16 OF 29 EMBASE on STN

ACCESSION NUMBER: 96310469 EMBASE

DOCUMENT NUMBER: 1996310469

TITLE: Enhanced tumorigenic behavior of glioblastoma cells expressing a truncated **epidermal** growth factor receptor is mediated through the Ras-Shc- Grb2 pathway.

AUTHOR: Prigent S.A.; Nagane M.; Lin H.; Huvar I.; Boss G.R.; Feramisco J.R.; Cavenee W.K.; **Huang H.-J.S.**

CORPORATE SOURCE: Ludwig Institute for Cancer Research, University of California,San Diego, CA 92093-0660, United States

SOURCE: Journal of Biological Chemistry, (1996) 271/41 (25639-25645).
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A mutant **epidermal** growth factor receptor (Δ **EGFR**) containing a deletion of 267 amino acids from the extracellular domain is common in human glioblastomas. We have previously shown that the mutant receptor fails to bind EGF, is constitutively phosphorylated, and confers upon U87MG glioblastoma cells expressing it (U87MG.Δ **EGFR**), an increased ability to form tumors in mice. Here we demonstrate that the constitutively phosphorylated Δ **EGFR** enhances growth of glioblastoma cells through increased activity of Ras: 1) there was an increase in the proportion of Ras present in the GTP- bound form, and 2) introduction of neutralizing anti-Ras 259 antibodies into U87MG and U87MG.Δ **EGFR** cells by microinjection inhibited DNA synthesis to the same low level in both cell populations. We also show that the truncated EGF receptor constitutively associates with the adapter proteins Shc and Grb2 which are involved in the recruitment of Ras to

activated receptors. Several derivatives of Δ **EGFR** containing single, or multiple mutations at critical autophosphorylation sites were constructed and used to demonstrate that the major Shc binding site is Tyr-1148, and that Grb2 association occurs primarily through Tyr-1068. We conclude that the increased tumorigenic potential of glioblastoma cells expressing the truncated EGF receptor is due at least in part to Ras activation presumably involving the Shc and Grb2 adapter proteins.

L12 ANSWER 17 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:409153 BIOSIS
DOCUMENT NUMBER: PREV200200409153
TITLE: A novel antibody directed to the **epidermal** growth factor receptor (**EGFR**) displays additive and synergistic anti-tumor activity when used in combination with standard **EGFR** therapeutics.
AUTHOR(S): Johns, Terrance Grant [Reprint author]; Luwor, Rodney; Perera, Rushika; **Cavenee, Webster**; Old, Lloyd; Burgess, Antony; Scott, Andrew
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Melbourne, VIC, Australia
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 580-581. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2002
Last Updated on STN: 31 Jul 2002

L12 ANSWER 18 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:185199 BIOSIS
DOCUMENT NUMBER: PREV199900185199
TITLE: Genetic basis of human glioma.
AUTHOR(S): **Huang, H.-J. S.**; Nagane, M.; Cavenee, W. K.
CORPORATE SOURCE: Ludwig Inst. Cancer Res., La Jolla, CA 92093-0660, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 743. print.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 May 1999
Last Updated on STN: 16 Jun 1999

L12 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:470488 BIOSIS
DOCUMENT NUMBER: PREV199800470488
TITLE: Tumorigenic enhancement by mutant **EGFR** mediated by threshold levels of constitutive **tyrosine** phosphorylation and unattenuated signalling.
AUTHOR(S): Cavenee, W. [Reprint author]; Nagane, M. [Reprint author]; Klingbeil, C.; Lin, H.; Nishikawa, R. [Reprint author]; Ji, X-D.; Huang, C.-M.; Gill, G. N.; Wiley, H. S.; **Huang, H.-J. S.** [Reprint author]
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Univ. Calif.-San Diego, San Diego, CA, USA
SOURCE: Journal of Pathology, (1998) Vol. 186, No. SUPPL., pp. 15A. print.
Meeting Info.: 17th Meeting of the Pathological Society of Great Britain and Ireland. Leicester, England, UK. July 1-3, 1998. Pathological Society of Great Britain and Ireland.
CODEN: JPTLAS. ISSN: 0022-3417.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 1998
Last Updated on STN: 30 Oct 1998

L12 ANSWER 20 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:422723 BIOSIS
DOCUMENT NUMBER: PREV199799721926
TITLE: Tumorigenic enhancement by mutant **EGFR** mediated by threshold levels of constitutive **tyrosine** phosphorylation and unattenuated signalling.
AUTHOR(S): Cavenee, W. [Reprint author]; Nagane, M. [Reprint author]; Klingbeil, C. [Reprint author]; Lin, H. [Reprint author]; Nishikawa, R.; Ji, X.-D.; Huang, C.-M.; Hill, G. N.; Wiley, H. S.; **Huang, H.-J. S.**
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Univ. Calif., San Diego, CA, USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 9, pp. A1448.
Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology. San Francisco, California, USA. August 24-29, 1997.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997

L12 ANSWER 21 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:232551 BIOSIS
DOCUMENT NUMBER: PREV199799531754
TITLE: Farnesyl protein transferase inhibitors preferentially inhibit growth of gliomas with truncated **EGFR** (DELTA-**EGFR**).
AUTHOR(S): Caday, C. G. [Reprint author]; Nanda, A.; Cavenee, W.; **Huang, H. J. S.**; Han, Y.
CORPORATE SOURCE: Neurosurgery, LSU Med. Cent., Shreveport, LA, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 351.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research. San Diego, California, USA. April 12-16, 1997.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jun 1997
Last Updated on STN: 2 Jun 1997

L12 ANSWER 22 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:490709 BIOSIS
DOCUMENT NUMBER: PREV199699213065
TITLE: Differential effects of **tyrphostin** AG 1478 on human glioma cells expressing truncated or wild-type **EGFR**.
AUTHOR(S): Han, Yuchun [Reprint author]; Nanda, Anil [Reprint author]; **Cavenee, Webster K.**; **Huang, H.-J. Su**; Caday, Cornelio G. [Reprint author]
CORPORATE SOURCE: Neurosurg., La. State Univ. Med. Cent., 1501 Kings Highway, Shreveport, LA 71130, USA
SOURCE: Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 946.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience. Washington, D.C., USA. November 16-21, 1996.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Nov 1996
Last Updated on STN: 10 Dec 1996

L12 ANSWER 23 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:258012 BIOSIS
DOCUMENT NUMBER: PREV199698814141
TITLE: Enhanced tumorigenicity of a common mutant **epidermal** growth factor receptor in human gliomas is conferred by elevated proliferation rate and reduced **apoptosis** rate.

AUTHOR(S): Nagane, M. [Reprint author]; Lin, H.; Coufal, F.; Cavenee, W. K.; **Huang, H.-J. S.**
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Univ. Calif., San Diego, CA, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 571.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research. Washington, D.C., USA. April 20-24, 1996.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 1996
Last Updated on STN: 31 May 1996

L12 ANSWER 24 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:411658 BIOSIS
DOCUMENT NUMBER: PREV199598425958
TITLE: **EGFR** gene amplification-rearrangement in human glioblastomas.
AUTHOR(S): Schwechheimer, Karl [Reprint author]; Huang, Su; **Cavenee, Webster K.**
CORPORATE SOURCE: Inst. Neuropathologie, Univ.-Gesamthochschule, Hufelandstr. 55, 45122 Essen, Germany
SOURCE: International Journal of Cancer, (1995) Vol. 62, No. 2, pp. 145-148.
CODEN: IJCNAW. ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 1995
Last Updated on STN: 27 Sep 1995
AB Immunostaining using an affinity-purified rabbit polyclonal antibody against the extracellular domain of the **epidermal**-growth-factor receptor (**EGFR**) showed over-expression occurring in a fraction of tumor cells in 17 out of 18 human glioblastomas and in a majority of cells in 7 of the 18. Southern-blotting technique using a full-length **EGFR** cDNA probe showed a variable degree of amplification in 10 of the 17 glioblastomas, which was associated with **EGFR** over-expression in each case. In 2 of the glioblastomas with **EGFR** gene amplification, a rearrangement of the gene affecting the extracellular domain of the receptor was identified and DNA sequence analyses revealed an identical deletion-rearrangement of 801 base pairs between exons 2 to 7, resulting in an in-frame fusion of exons 1 and 8.

L12 ANSWER 25 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:605319 CAPLUS
DOCUMENT NUMBER: 140:376
TITLE: Growth suppression of intracranial xenografted glioblastomas overexpressing mutant **epidermal** growth factor receptors by systemic administration of mAb 806, a novel monoclonal antibody directed to the receptor
AUTHOR(S): Mishima, Kazuhiko; Nishikawa, Ryo; Mastutani, Masao; **Huang, H.-J. Su; Cavenee, Webster K.**
CORPORATE SOURCE: Dep. Neurosurgery, Saitama Med. Sch., Japan
SOURCE: Posutoshikuensu Jidai ni Okeru Noshuyo no Kenkyu to Chiryo, [Nippon Noshuyo Kanferansu Ronbunshu], 10th, Beppu, Japan, Dec. 2-4, 2001 (2002), Meeting Date 2001, 193-199. Editor(s): Tabuchi, Kazuo; Shiraishi, Tetsuya. Kyushu Daigaku Shuppankai: Fukuoka, Japan.
CODEN: 69EHCC; ISBN: 4-87378-743-2
DOCUMENT TYPE: Conference
LANGUAGE: Japanese
AB. A mutant **epidermal** growth factor receptor (variously called Δ **EGFR** or EGFRvIII) containing a deletion of 267 amino acids of the extracellular domain is frequently highly expressed in human malignant gliomas. We tested the efficacy of a novel monoclonal anti-Δ **EGFR** antibody, mAb 806, on the growth of intracranial xenografted gliomas in nude mice. Systemic treatment with mAb 806 significantly reduced the volume of tumors and increased the survival of mice bearing xenografts of U87MG.Δ **EGFR** or LN-Z308.Δ **EGFR** gliomas, each of which expresses high levels of AEGFR. In contrast, mAb 806 treatment was ineffective with mice bearing the parental U87MG tumors which expressed low levels of endogenous wild-type **EGFR** or U87MG.DK tumors which expressed high levels of kinase-deficient Δ

EGFR. A slight increase of survival of mice xenografted with a wild-type **EGFR**-overexpressing U87MG glioma (U87MG.wtEGFR) was effected by mAb 806 concordant with its weak cross-reactivity with such cells. Treatment of U87MG.Δ **EGFR** tumors in mice with mAb 806 caused decreases in both tumor growth and angiogenesis, as well as increased **apoptosis**. Mechanistically, in vivo mAb 806 treatment resulted in reduced phosphorylation of the constitutively active Δ **EGFR** and caused down regulated expression of the apoptotic protector, Bcl-XL. These data provide preclin. evidence that mAb 806 treatment may be a useful biotherapeutic agent for those aggressive gliomas expressing Δ **EGFR**.

L12 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:888893 CAPLUS
DOCUMENT NUMBER: 137:383800
TITLE: Chimeric and humanized antibodies and fragments specific to glycosylated EGF receptor for cancer diagnosis and therapy
INVENTOR(S): Old, Lloyd J.; Johns, Terrance Grant; Panousis, Con; Scott, Andrew Mark; Renner, Christoph; Ritter, Gerd; Jungbluth, Achim; Stockert, Elisabeth; Collins, Peter; **Cavenee, Webster K.**; Huang, Huei-Jen; Burgess, Anthony Wilks; Nice, Edouard Collins
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 245 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092771	A2	20021121	WO 2002-US15185	20020513
WO 2002092771	A3	20031127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1392359	A2	20040303	EP 2002-739258	20020513
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
US 2001-290410P P 20010511
US 2001-326019P P 20010928
US 2001-342258P P 20011221
WO 2002-US15185 W 20020513

AB The invention relates to specific binding members, particularly antibodies and active fragments thereof, which recognize an aberrant post-translationally modified, particularly an aberrant glycosylated form of the **EGFR**. The binding members, particularly antibodies and fragments thereof, of the invention do not bind to **EGFR** on normal cells in the absence of amplification of the wild- type gene and are capable of binding the de2-7 **EGFR** at an epitope which is distinct from the junctional peptide. Antibodies of this type are exemplified by the novel antibody 806 whose VH and VL sequences are illustrated as SEQ ID Nos: 2 and 4 and chimeric antibodies thereof as exemplified by ch806. The antibodies may also be radiolabeled for immunodiagnosis and radioimmunotherapy of cancers, especially brain-resident cancers.

L12 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:906210 CAPLUS
DOCUMENT NUMBER: 136:15231
TITLE: Methods using a **tyrosine** kinase inhibitor to modulate the resistance of cells to **apoptosis** mediated by mutant **epidermal** growth factor receptors
INVENTOR(S): **Huang, H.-J. Su; Nagane, Motoo; Cavenee, Webster K.**; Levitzki, Alexander; Gazit, Aviv

PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001051628	A1	20011213	US 1998-71541	19980504
PRIORITY APPLN. INFO.:			US 1998-71541	19980504

AB Methods and compns. are provided for enhancing the activity of various therapeutic agents that induce **apoptosis** by modulating the **apoptosis**-inhibiting effects of the expression products of mutant **epidermal** growth factor receptor (**EGFR**) genes. Methods and compns. of particular use in the treatment of cancers, e.g. glioma, that express such a mutant **EGFR** gene are provided. The methods of the invention use a **tyrosine** kinase inhibitor (e.g. **tyrphostin** AG1478) in combination with an **apoptosis** -inducing therapeutic agent (e.g. cisplatin).

L12 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:790262 CAPLUS
DOCUMENT NUMBER: 138:336121
TITLE: Growth suppression of intracranial xenografted glioblastomas overexpressing mutant **epidermal** growth factor receptors by systemic administration of monoclonal antibody (mab) 806, a novel monoclonal antibody directed to the receptor. [Erratum to document cited in CA135:255801]
AUTHOR(S): Mishima, Kazuhiko; Johns, Terrance G.; Luwor, Rodney B.; Scott, Andrew M.; Stockert, Elisabeth; Jungbluth, Achim A.; Ji, Xiang-Dong; Suvarna, Padma; Voland, Joseph R.; Old, Lloyd J.; **Huang, H-J. Su; Cavenee, Webster K.**
CORPORATE SOURCE: Ludwig Institute for Cancer Research, San Diego Branch, University of California at San Diego, La Jolla, CA, 92093-0660, USA
SOURCE: Cancer Research (2001), 61(20), 7703-7705
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The correct versions of Figures 4 and 5 are given.

L12 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:241782 CAPLUS
DOCUMENT NUMBER: 114:241782
TITLE: Genes for **epidermal** growth factor receptor, transforming growth factor α, and **epidermal** growth factor and their expression in human gliomas in vivo
AUTHOR(S): Ekstrand, A. Jonas; James, C. David; **Cavenee, Webster K.**; Seliger, Barbara; Pettersson, Ralf F.; Collins, V. Peter
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Stockholm, S-104 01, Swed.
SOURCE: Cancer Research (1991), 51(8), 2164-72
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anomalies of the **epidermal** growth factor receptor (**EGFR**) gene, including amplification, rearrangement, and overexpression, have been reported in malignant human gliomas in vivo. In vitro glioma cell lines coexpress **EGFR** and at least one of its ligands, transforming growth factor α, suggesting the existence of an autocrine growth stimulatory loop. The tumor tissue from 62 human glioma patients was examined for the structure and quantity of the **EGFR** gene and its transcripts, as well as the quantity of the receptor protein. In addition, the genes and transcripts coding for the pre-pro forms of **epidermal** growth factor and transforming growth factor α, the 2 endogenous **EGFR** ligands were examined **EGFR** gene amplification was detected in 16 of the 32 malignancy grade IV gliomas (glioblastoma) studied (50%), but only in 1 of 30 gliomas of lesser malignancy grade (I-III). All tumors with an amplified gene overexpressed **EGFR** mRNA. More than one-half (62.5%) of the glioblastomas with

amplified **EGFR** genes also showed coamplification of rearranged **EGFR** genes and concomitant expression of aberrant mRNA species. Overexpression, without gene amplification, was observed in some of the low-grade gliomas, and aberrant **EGFR** transcripts were also seen in some cases without gene amplification or detected gene rearrangements. MRNA expression for one or both of the pre-pro forms of the ligands was detected in every tumor studied. Thus, several mechanisms for the activation of the **EGFR**-mediated growth stimulating pathway are possible in human gliomas in vivo; expression of a structurally altered receptor that may have escaped normal control mechanisms; and/or auto-, juxta-, or paracrine-stimulating mechanisms involving coexpression of receptor and ligands, with or without overexpression of the receptor.